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The Clinical Research Office of the Endourology Society (CROES) multicentre randomised trial of narrow band imaging-assisted transurethral resection (TURBT) versus conventional white light-assisted TURBT in primary non-muscle-invasive bladder cancer patients: trial protocol and 1-year results

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Abstract

***Background*:** White light (WL) is the established imaging modality for transurethral resection of bladder tumour (TURBT). Narrow band imaging (NBI) is a promising addition.

***Objectives*:** To compare 12-mo recurrence rates following TURBT using NBI versus WL guidance.

Design, setting, and participants: The Clinical Research Office of the Endourology Society (CROES) conducted a prospective, randomised, single-blind, multicentre study. Patients with primary non-muscle-invasive bladder cancer (NMIBC) were randomly assigned 1:1 to TURBT guided by NBI or by WL.

Intervention: TURBT for NMBIC using NBI or WL.

Outcome measurements and statistical analysis: 12-mo recurrence rates were compared by chi-square tests and survival analyses.

Results and limitations: Of the 965 patients enrolled in the study, 481 patients underwent WL-assisted TURBT and 484 patients received NBI-assisted TURBT. Of these, 294 and 303 patients, respectively, completed 12-mo follow-up, with recurrence rates of 27.1% and 25.4%, respectively (p = 0.585, Intention-to-treat (ITT) analysis). In patients at low risk for disease recurrence, recurrence rates at 12-mo were significantly higher in the WL group compared with the NBI group: 27.3% vs 5.6% (p = 0.002, ITT analysis). Although TURBT took longer on average with NBI plus WL compared with WL alone (38.1 min vs 35.0 min; p = 0.039, ITT; 39.1 vs 35.7 min; p = 0.047, Per protocol (PP) analysis), lesions were significantly more often visible with NBI than with WL p =0.033). The frequency and severity of adverse events were similar in both treatment groups. Possible limitations were: lack of

uniformity of surgical resection, data on smoking status, central pathology review, and specific date regarding adjuvant intravesical instillation therapy.

Conclusions: NBI and WL guidance achieved similar overall recurrence rates 12-mo after TURBT in patients with NMIBC. NBI-assisted TURBT significantly reduced the likelihood of disease recurrence in low-risk patients.

Patient summary: Using a narrow band imaging technique might provide greater detection of bladder tumours and subsequent treatment, leading to reduced recurrence in low-risk patients

1. Introduction

The standard intervention following initial diagnosis of non-muscle invasive bladder cancer (NMIBC) is transurethral resection of bladder tumour (TURBT) with white light (WL) imaging guidance [1]. However, small bladder tumours, such as flat malignant lesions (carcinoma *in situ*; CIS) or small papillary tumours, can be missed [2,3]. These undetected or incompletely resected tumours with diffuse borders can recur, with some becoming invasive, which emphasises the need for improved techniques to detect NMIBC. Moreover, some authors consider the majority of early recurrences to result from initial surgical failure [4].

Research has focused on improved methods of detection, including narrow band imaging (NBI), a high-resolution endoscopic optical technique. Filtering white light into two bandwidths of 415 and 540 nm, which are absorbed by haemoglobin, enhances the contrast between normal urothelium and hypervascular cancer tissue. NBI enhances the submucosal capillaries and, because bladder tumours are well vascularised with densely arranged irregular vessels, the contrast between tumours and normal mucosa is improved.

NBI has proved more effective than conventional WL cystoscopy [5,6]. Currently, there is limited experience with NBI in detecting bladder cancer but early results are encouraging [7–9]. The aim of the present study was to compare the efficacy and safety of TURBT using NBI or WL cystoscopy in NMIBC. We hypothesize that use of NBI at the time of TURBT will decrease recurrence rates at one year, compared to WL cystoscopy alone.

2. Methods

2.1. Study design and participants

The CROES NBI Study was a prospective, randomised, single-blind, multicentre trial, which was conducted at 26 specialist urological centres in 16 countries from August 2010 to October 2014. The study included patients aged 18 yr or older scheduled for treatment of a primary (initially diagnosed) NMIBC; those eligible for inclusion were patients scheduled for TURBT with papillary bladder tumour(s) detected by imaging or cystoscopy or those scheduled for random biopsies and/or TURBT because of bladder lavage fluid or voided urine cytology with malignant (G3) cells. Exclusion criteria included: the presence of tumours in the upper urinary tract; muscle invasive bladder tumour; previous irradiation of the pelvis; gross haematuria (defined as heavy bladder bleeding resulting in marked amounts of blood in the urine) which might interfere with cystoscopy at the time of TURBT; participation in other clinical studies with investigational drugs either concurrently or within the last 30 d; pregnancy; and any condition associated with a risk of poor protocol compliance (for example patients with severe comorbidity interfering with thorough follow-up).

Patients eligible for the study were contacted through medical staff and provided with verbal and written information. All participants were required to sign informed consent forms. The study was approved by the Institutional Review Board of each participating centre and carried out according to the guidelines of good clinical practice [1]. The trial was registered in The Netherlands Trial Register (NTR3645). All data were collected through an on-line electronic data management system (https://www.croes-dms.org). Access to this secure system was restricted to each centre investigator and CROES data managers and enabled by individual passwords.

2.2. Randomisation

After enrolment, patients were randomly allocated in a 1:1 ratio to parallel control (WL) and intervention (NBI) arms. Randomisation was conducted by means of a concealed computer-generated random sequence of numbers using permuted blocks and stratified for: multiplicity (single or multiple tumours), macroscopic findings (papillary or solid/flat tumour) and age (either ≥ or < 40 yr). The process was implemented through the on-line data management system. Patients were blinded for the treatment arm they were randomised to.

2.3. Procedures and follow-up

In the out patients clinic, patients diagnosed as bladder tumour using WL cystoscopy were evaluated for inclusion and exclusion criteria, and preoperative data were collected, including age, gender, weight, height, ethnicity, anticoagulation therapy, co-morbidity, symptoms, urinalysis, urine culture and cytology, and upper urinary tract imaging results.

In the operating room, eligible patients in both arms of the study underwent cystoscopy evaluation of the bladder and indication of all tumours using WL cystoscopy. Registration of lesions on the bladder chart included presence of lesion, type (papillary, or flat), number of lesions and location (bladder neck anterior, trigone, around ureteric orifice right, around ureteric orifice left, posterior floor, right lateral wall, cranial wall, left lateral wall, dome, anterior bladder wall and bladder neck posterior). Patients in the WL arm were then treated according to the normal hospital routines, i.e. complete resection of all papillary lesions, and biopsy and subsequent complete fulguration of all flat lesions including suspicious areas with WL. In patients

of the NBI arm, following documentation of tumours visualized under WL and prior to resection, the bladder tumours were remapped on the bladder diagram under NBI. Then, complete resection of all papillary lesions, and biopsies and subsequent complete fulguration of all flat lesions including suspicious areas were conducted with NBI. Operative factors recorded for all patients included the date and duration of surgery, antibiotic prophylaxis, type of resection, visibility of lesion, performance of routinely random biopsies, tumour location and intraoperative complications. Postoperatively, the duration of catheterization and hospital stay, antibiotics use, pathological characteristics and complications were noted. Surveillance WL cystoscopy was planned to be done in all patients at the 3- and 12-mo follow-up visits, with histological confirmation to assess recurrence. If recurrent CIS was suspected by urine cytology, biopsy was performed to confirm CIS histologically

2.4. Outcomes

The primary outcome measure was recurrence rate at 1 yr. A recurrence was defined as the new occurrence of a bladder cancer at the same or different site to the index cancer. Secondary outcomes were tumour recurrence at first follow-up (3-mo post-TURBT) or presence of recurrent/residual tumour at previously resected locations (within 60 d of initial TURBT). Basically, re-resection was performed within 60 d of initial TURBT with WL in both groups for patients with pT1 tumour, whose initial resected specimen did not contain sufficient muscle layer and those who were suspected of incomplete resection regardless of tumour stage. The local pathologist conducted histological assessment of both biopsied tissue and samples from

resected lesions. The study also assessed perioperative morbidity (within the first 30 d of TURBT) using the Clavien-Dindo score [10].

Adverse events (AEs) were assessed and recorded for 7 d after the initial TURBT procedure or until resolution. They were also recorded at the 3- and 12-mo follow-up. AE severity was graded on a 5-point scale according to the US National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 [11].

2.5. Statistical analyses

The expected recurrence rate in the WL-assisted TURBT group was 35% [12]. To detect a clinically relevant difference in recurrence detection rates of ≥10% at a 5% significance level and a power of 80%, the required sample size per treatment was calculated to be 329 patients (658 patients in total). To allow for a non-compliance rate of 25% and a 15% loss of patients who could be diagnosed with a pT0 or ≥pT2 tumour later in the process, and assuming no crossover and no differential loss to follow-up between arms, the calculated sample size was increased proportionately resulting in a target recruitment of 946 patients.

The primary efficacy analysis was performed on the intention-to-treat (ITT) population, which included those participants who were correctly randomised and were willing to participate in the study. A per protocol (PP) analysis was also performed on the study population who were correctly randomised, were willing to participate in the study and had no protocol violations. Pearson’s chi-square analysis was used for dichotomous or categorical variables. When the Pearson’s chi-square assumptions were not met, the Fisher’s exact test was used. Analysis of variance

(ANOVA) was used for continuous variables to compare characteristics and outcomes between the two groups. Survival analysis was performed using the log-rank test, and shown in Kaplan Meier curves; both analyses used patient information up to the point at which censoring occurred. As all data were not available for every patient, last observation carried forward (LOCF) was also applied. The level of statistical significance was set at $p < 0.05$. Percentages were calculated and analyses performed on available data. A sub-analysis was conducted according to disease status, including low, intermediate and high-risk European Organisation for Research and Treatment of Cancer risk classification [12].

3. Results

Between August 2010 and October 2014, 981 patients at 28 centres in 14 countries (Appendix 1) were assigned to the two study groups. The trial profile is shown as a CONSORT flow diagram in Figure 1. Sixteen patients at two centres were subsequently excluded because the quality of the data could not be assured; shortly after the start of the study these centres changed to using equipment other than NBI. The ITT population thus comprised 481 patients randomised to the WL group and 484 patients randomised to the NBI group. Following histopathological examination, 66 patients had no available pT, or pT could not be assessed (pTx). 78 patients were excluded for muscle-invasive disease (category pT2 or higher) and absence of disease (pT0) was found in 77 patients who were then also excluded. One further patient received no intervention (surgery), leaving 365 patients in the WL group and 379 patients in the NBI group available for the PP analysis.

The baseline characteristics of the patients included in this study are shown in Table 1. There were no significant differences in terms of tumour location, tumour number and tumour size between the patients in the WL and the NBI groups for the ITT and PP populations.

Surgery time including resection time and time for mapping out the bladder tumour was significantly longer if NBI guidance was used compared with WL (p = 0.039, ITT); this difference was also significant in the PP analysis (p = 0.047) (Table 2). A lesion was significantly more often visible in NBI compared with WL (p = 0.033, ITT). Tumour location in the dome region was significantly more frequent in the NBI group (13.9%) compared with the WL group (9.6%) for the ITT populations (p = 0.041). There were no other significant differences between the two groups in regard to tumour characteristics, operative factors or peri-operative complications (Table 2).

LOCF data on the frequency of re-resection (re-TURBT) and recurrence at re-TURBT are shown in Table 3 and indicate a similar frequency in the two treatment groups. A significantly lower rate of recurrence was found in low-risk patients (pTa, Grade 1, < 30 mm, and no CIS) [1] in the NBI group compared with the WL group, which was evident after 3-mo (0 vs 15.1%; p = 0.006) and 12-mo (5.6% vs 27.3%; p = 0.002) of follow-up. Similar proportions of patients completed 12-mo follow-up (n = 294 [62.6%] WL group; n = 303 [61.1%] NBI group, ITT analysis). Recurrence rates reported were 27.1% (n = 109) and 25.4% (n =104) in the WL and NBI groups , respectively (p = 0.585; ITT analysis).

Analysis of recurrence vs time showed diverging recurrence-free survival rates for low-risk patients in the two treatment groups from 60–70 d follow-up (Fig. 2B), in

contrast to the similar rates found throughout follow-up in intermediate-risk, high-risk and all-patient groups (Fig. 2C, 2D and 2A, respectively).

There were no significant differences between treatment groups in the number and severity of AEs (Appendix Table 1).

4. Discussion

Overall, this study found no difference in tumour recurrence between NBI-assisted TURBT and WL-assisted TURBT at 12-mo follow-up, but did find a significantly lower rate of recurrence in low-risk patients. Most of the recurrence in these patients may be due to small tumours, which are often overlooked during the TUR. We hypothesise that NBI provided greater visualisation of such overlooked lesions, therefore reducing the recurrence rate in low-risk patients. The better 3-mo recurrence-free rate in the NBI group for low risk patients may be reflective of a more complete superficial (but not deep) resection by using NBI. In contrast, the recurrence in intermediate or high-risk patients may be caused by not only development of overlooked small tumours but also regrowth of high-grade tumour cells disseminated during TUR [13]. NBI, through more precise detection and resection of small tumours, may be able to decrease recurrence rate, but it is unlikely to influence regrowth of disseminated high-grade tumour cells. Consequently, the benefit of NBI was clear in the low-risk group but not in intermediate- or high-risk groups.

Compared with published studies, the present study has a fundamental difference in its design. The inclusion of only those patients with primary tumours enables the

evaluation of a specific test in a given population. In addition, previous studies have primarily included patients with (highly) recurrent papillary tumours that are overrepresented by low risk disease. In contrast, in the present study, there was a larger patient population with intermediate- and high-risk disease (equally distributed in the WL and NBI groups). In line with this, in the present work the overall recurrence rate was significantly lower than was initially expected.

The CROES Council approved all centres participating in this study and the principal investigator at each study site was a member of the Endourological Society. This high standard of uro-oncological engagement and expertise within the study is likely to have ensured efficient tumour identification and thorough resection (particularly of larger tumours) with either imaging modality. Surgeon experience and technical ability both affect the clinical outcome (including recurrence) after TURBT of new NMIBC [14], although the reliability of bladder tumour evaluation by NBI cystoscopy has been reported to be unaffected by urologists' prior experience [15]. Furthermore, it is considered within the field that familiarity with image-enhancement modalities (such as NBI) improves a surgeon's ability to detect small lesions with WL alone. We interpret the emergence of a difference in recurrence rate between NBI-assisted TURBT and WL-assisted TURBT only in low-risk patients as indicative of the higher efficacy of NBI in visualising smaller tumours, but we accept the possibility of observer bias e.g. double mapping favouring NBI as a limitation of this single-blind study. Furthermore, in recent years, the quality of WL imaging equipment has also improved considerably.

Assuming recurrence was caused by a tumour undetected during the first resection [13], the difference in rate of recurrence in low-risk patients between treatments evident at 3-mo post-intervention was unexpected. By including patients with primary NMIBC, we anticipated that many tumours undetected initially would still be too small to detect 3-mo after initial TURBT and that recurrences in this patient group would be detectable only after longer term follow-up.

The reduction in recurrence rate in low-risk patients has obvious clinical benefits and is likely to be accompanied by favourable economic effects; lower recurrence rates with NBI compared with WL would reduce the need for further TURBTs and the frequency of surveillance [16]. Furthermore, lesions initially overlooked by WL that subsequently become visible at the 3-mo check cystoscopy would be incorrectly classed as recurrence. Management of patients with recurrence includes closer surveillance and further TURBT, resulting in increasing cost compared with identification during the preliminary examination with NBI. While the cost of the TURBT procedure is likely to be similar for NBI and WL, longer operating room use with NBI procedures in certain patients would add to resource use costs. The additional time needed is only an average of 3 min per procedure, which can be balanced against the lack of a significant difference in the frequency and the severity of grades of peri-operative complications and AEs in the two treatment groups.

Several previous studies have reported improved detection of bladder tumours with NBI cystoscopy compared with standard WL cystoscopy [8,17–21]. Recent meta-analyses of clinical trials in bladder cancer show that NBI provides comparable or higher diagnostic precision than WL [9,22]. Li et al calculated that an additional 17%

of patients (95% CI 10–25%) and an additional 24% of tumours (95% CI 17–31%) were detected by NBI [22]. The small number of clinical trials that have reported disease recurrence show that the use of NBI vs WL improves recurrence rates by 15–32%, with time to recurrence of 29 and 13-mo, respectively [13,23–25]. The present study addresses the relative lack of prospective recurrence data for NBI. Further support for the benefits of improved visualisation of bladder tumours can be found in some studies of photodynamic diagnosis (PDD), which show recurrence-free rates at 12-mo 11–27% higher with PDD than with WL and the difference in outcome between the two techniques extended over several years [16,26]. In other studies, however, higher tumour detection rates with PDD did not translate into lower rates of NMIBC recurrence [27].

In addition to earlier mentioned limitations, other possible limitations of the present study include: 1. the lack of documentation of smoking status/ongoing environmental exposures that may increase the risk of urothelial carcinoma; 2. the lack of central review pathology; 3. Lack of documentation in the use of adjuvant intravesical instillation therapy. Furthermore, we are aware of the substantial number of patients who did not receive the 3 or 12-mo follow-up cystoscopies and loss to follow-up in this study. However, this was taken into account in the sample size calculation.

In summary, this large, prospective, multicentre, randomised clinical trial in patients with primary NMIBC showed that, while NBI and WL guidance achieved similar overall recurrence rates after TURBT at 12-mo follow-up, NBI-assisted TURBT significantly reduced disease recurrence in low-risk patients (pTa, Grade 1, <30 mm,

and no CIS). This finding supports the use of NBI guidance as an alternative to the current standard approach involving WL.

Figure legends

Fig. 1 – Study flow chart. ITT = intention-to-treat. PP = per protocol. No cystoscopy: follow-up performed without cystoscopy. Not performed: follow-up at certain moment not performed. Lost to follow-up: Patient received no further follow-up at all. Not available: no data available.

Fig. 2 – Survival curves for no recurrence over a 12-mo follow-up period for the intention-to-treat population and risk subgroups following white-light- (WLI) or narrow band imaging- (NBI) assisted transurethral resection of bladder tumour. (A) all patients; (B) low-risk patients; (C) intermediate-risk patients; and (D) high-risk patients. Patients were stratified into risk groups using tumour characteristics according to European Association of Urology Guidelines [1]. CI = confidence interval.

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